

REMARKS

Upon entry of the above amendments, claim 1 to 3, 6 to 8, 11 to 13 and 15 will be pending in the present application. Applicants cancelled claims 4, 5, 9, 10 and 14 without prejudice to the subject matter contained therein. Applicants amended claims 1 to 6 and 11 to more clearly define the present invention and to comply with the restriction requirement. Applicants added new claim 15 which is supported by original claim 14. The specification provides support for the amendments. No new matter has been introduced by the instant amendments.

Rejection under 35 USC §112, second paragraph:

Claims 1-5, 7 and 8 stand rejected under 35 USC §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Examiner objected to the term "linker" for being indefinite. Applicants respectfully disagree. However to expedite prosecution, Applicants amended the definition of Q and brought in the limitation of claim 2 into claim 1.

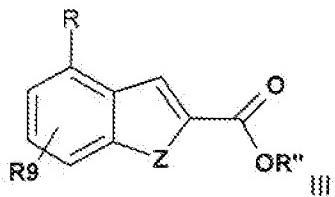
In view of the amendment, Applicants respectfully request withdrawal of the 35 USC §112, second paragraph rejection.

Rejection under 35 USC §112, first paragraph:

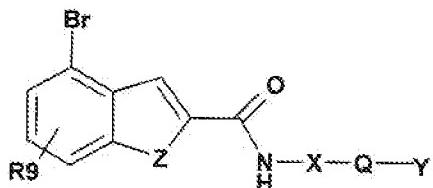
1. Claims 1-5, 7 and 8 stand rejected under 35 USC §112, first paragraph as allegedly being non-enabled for the prodrugs. Applicants deleted the term "prodrugs" in claim 1 and 2.

2. Claims 1-5, 7 and 8 stand rejected under 35 USC §112, first paragraph as allegedly being non-enabled for compounds where R is other than alkyl and benzofuran optionally substituted with Cl, R9 is other than H, Y is other than azepanyl, piperidinyl, pyranyl, optionally substituted with hydroxy, and X being other than unsubstituted cyclohexyl or phenyl. Applicants respectfully disagree.

The specification discloses on pages 22 and 23 and in the experimental section, that compounds of the invention were prepared according to a common carboxylic acid or ester intermediates (III) which undergo amide coupling reaction, which is well known reaction in the chemical art.



Additionally, the specification discloses on page 23 and in the experimental section that the group R can be introduced by displacement of a bromo substituent of intermediate VI. Numerous conditions are known in the chemical art. Example 157 also discloses one method of doing so, being the Suzuki coupling reaction using boronic acids. The Suzuki couplings conditions are very well known to be applicable to a large range of aryl boronic acids and heteroaryl boronic acids. Furthermore, a large numbers of commercially available boronic acids are readily available.



(VI)

Additionally, specific examples of compounds of Formula I or II wherein R is hydroxy, optionally substituted alkoxy (i.e. Methoxy, cyclopropylmethoxy, isobutoxy, cyclopentylmethoxy, furan-3-ylmethoxy, benzofuran-3-ylmethoxy, 4-methyl-pentyloxy, 1,2-dimethylpropoxy), heteroaryl such as pyridine (i.e. several examples of optionally substituted pyridine) or benzo[1,3]dioxol-5-yl, aryl such as phenyl (i.e. several example of optionally substituted phenyl), aryloxy (i.e. phenoxy), arylalkyloxy (i.e. benzyloxy), heteroaryloxy (i.e. 6-chloro-pyridin-2-yloxy) are disclosed. Applicants only cited a few representative specific examples for some of R variables listed above.

Applicants amended the definition of R9 as suggested by the Examiner.

Applicants amended the definition of Y to the list of variables provided on page 5 of the specification.

Applicants amended the definition of X and Z to comply with the restriction requirement.

The substituents for each variable are exemplified or are those typically considered by someone of ordinary skill in the art.

Applicants assert that in view of the above arguments, the claims as amended are fully supported by the specification and by the examples.

3. Claims 4 and 5 stand rejected under 35 USC §112, first paragraph as allegedly being non-enabled for binding to CCR2 and CCR5 enzymes.

Examiner also argues that there is no enablement for the method of treatment of autoimmune and inflammatory diseases. Applicants traverse this broad assertion.

The Examiner argues that at the time the invention was made, the treatment of autoimmune and inflammatory diseases was not well developed in the state of the prior art.

Applicants respectfully disagree that the instant claims are not enabled. The test of enablement is whether one reasonably skilled in the art, following the teaching of the patent specification coupled with information known in the art at the time the patent application was filed, could make or use the invention without undue experimentation. *U.S. v. Electronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Field v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988), and *In re Jackson*, 217 U.S.P.Q. 804, 807 (1982).

Applicants would like to direct the Examiner's attention to the review article in *immunology and cell Biology* (1999), 77, 469-475 on chemokines and chemokine receptors in infectious diseases.

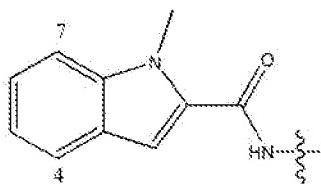
The above reference indicates that the correlation between chemokine receptor antagonists and autoimmune and inflammatory diseases was well established in the art at the time the application was filed. Applicants provided, on pages 213-215 of the specification, in-vitro data and protocols for measuring CCR2 and CCR5 activity in a binding and functional assay. Ranges of activities are provided for compounds of Formula I in various assays on pages 213-215. Therefore Applicants assert that a skilled person in medicinal chemistry could use the compounds of the invention for the treatment of autoimmune and inflammatory diseases without undue experimentation.

Applicants respectfully request withdrawal of the 35 USC §112, first paragraph rejections.

Rejection under 35 USC §102:

Claims 1, 2, 4, 5, 7 and 8 stand rejected under 35 USC §102(e) as being anticipated by US 7,078,419. Examiner cited several compounds from the US'419 which allegedly anticipate the claims of the instant invention. Applicants respectfully disagree.

The instant invention discloses compounds containing an indole wherein the R substituent in the 4-position of the indole. US '419 discloses compounds in which R is in the 7-position of the indole.



Therefore, none of the compounds of US '419 anticipate the instant claims.

Applicants respectfully request withdrawal of the 35 USC §102(e) rejection.

Rejection under 35 USC §103:

Claims 1, 2, 4, 5, 7 and 8 stand rejected under 35 USC §103(a) as being obvious over US 6,465,485. Examiner asserts that US '485 teaches positional isomer of compounds of the instant invention. Examiner asserts that compounds of US '485 contain an O-alkyl at the 6-position versus Applicants compound's O-alkyl at the 4-position. Examiner also states that US '485 teaches that 3,4-dihydroquinolinyl can be substituted with an alkoxy at any position of the phenyl ring.

Applicants respectfully disagree. US '485 discloses compounds wherein the Y group of the instant invention is 3,4-dihydroisoquinoline and wherein the A group can be a large number of alternatives, including indole. The instant invention as claimed do not cover compounds in which Y is dihydroisoquinoline. Furthermore, the teaching of US'485 with respect to the position of the alkoxy group on the dihydroisoquinoline, refers to the position of substituents on group Y of the instant invention and not on the indole of the instant invention.

Applicants also respectfully disagree that it is well established that positional isomers are *prima facie* obvious even in the absence of teaching to modify. "For a claimed compound to be *prima facie* obvious over the prior art compound with structural similarity, the prior art must suggest making the specific structural modifications necessary to arrive at the claimed invention." *Takeda v alphapharm*, 492 F. 3d 1350. Applicants assert that there is no motivation to replace dihydroisoquinoline group (limiting feature of US '485) with the Y group of the instant invention. Furthermore, there is no motivation to move the methoxy group from the 5-position of the indole to the 4-position of the indole. Someone of ordinary skill in the art would have had no motivation to combine several structural modifications in order to arrive at the instant claimed invention.

Additionally, "an obviousness argument based on structural similarity between the claimed and prior art compounds clearly depends on the preliminary finding that one of ordinary

skill would have selected the prior art compound as a lead compound". In this case, there was no motivation for someone of ordinary skill to select any compound from US '485 as lead compound for structural modification. US '485 discloses compounds which are dopamine receptor ligands useful for the treatment of antipsychotic agents. Someone of ordinary skill in the art in the search of a CCR2 and/or CCR5 antagonists for the treatment of anti-inflammatory diseases, would have had no reason to select an antipsychotic agent as a lead compound. Furthermore, there is no motivation or suggestion to move the alkoxy group from position 5 to position 4 of the indole, combined with the replacement of the dihydroisoquinoline group with a Y group of the invention. Finally, there would have been no expectation of success: It would not be expected that by combining several structural modifications, one could change a dopamine receptor ligand into a CCR2 and/or CCR5 antagonist.

Applicants respectfully request withdrawal of the 35 USC §103(a) rejection.

Conclusion:

Applicants have addressed each and every issue set forth by the Examiner. Applicants respectfully submit that the claims are in good condition for allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 617-871-5027.

Respectfully submitted,



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